Focus on post-resuscitation care

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In patients who are admitted to an intensive care unit after resuscitation from cardiac arrest (CA) mortality attains 60-70% [1]. Two-thirds of these deaths are due to hypoxic-ischaemic brain injury (HIBI) and occur mainly after 72 h, as a result of withdrawal of life sustaining treatment (WLST) based on prediction of a poor neurological outcome [2]. The second most common cause of post-resuscitation death, especially in the very early phase after return of spontaneous circulation (ROSC) is circulatory failure. Current research on post-resuscitation care focuses on interventions aimed at reducing these two important causes of morbidity and mortality after CA.

Temperature management, coronary angiography

Targeted temperature management (TTM) for 24 hours after ROSC is recommended to reduce HIBI, but the optimal temperature is unclear [2, 3]. A recent multicentre pilot randomised clinical trial (RCT) assigned comatose survivors of witnessed out-of-hospital CA (OHCA) from ventricular fibrillation/ventricular tachycardia (VF/VT) to TTM at 32°C (n = 52), 33°C (n = 49) or 34°C (n = 49); see **Table 1**). Cooling was tolerated well, but 90-day neurological outcome did not differ among groups [4]. Patients cooled to 32°C had lower rates of WLST due to severe HIBI. Cooling to this temperature may be the focus of further research.

Immediate coronary angiography is recommended in survivors of OHCA with ST-segment elevation (STE) on their electrocardiogram [1], but the benefit of this intervention after non-STE OHCA is uncertain. The multicentre COACT trial, which included 552 non-STE patients resuscitated from VF/VT OHCA, showed that an immediate vs. a delayed angiography strategy (median [IQR] 2.3 [1.8–3.0] vs. 121.9 [52.0–197.3] hours from arrest) was not associated with higher 90-day survival (64.5 vs. 67.2%; p=0.51) [5]. Acute unstable coronary lesions were found in less than 20% of the patients in this trial. Future studies may focus on non-STE patients more likely to benefit from immediate percutaneous coronary interventions (PCI). A recent retrospective study on 1,410 resuscitated OHCAs also suggested that only patients with low risk of in-hospital death according to the Cardiac Arrest Hospital Prognosis score benefited from early PCI [6].

Oxygenation and ventilation, cerebral perfusion

Observational evidence suggests that hyperoxia may be associated with worse neurological outcome after CA, while mild hypercapnia and higher mean arterial blood pressure (MAP) may be associated with better neurological outcome [2]. The COMACARE pilot multi-centre RCT evaluated the feasibility of targeting low-normal (4.5–4.7 kPa) vs. high-normal (5.8–6.0 kPa) $PaCO_2$, normoxia (PaO_2 10–15 kPa) vs. moderate hyperoxia (PaO_2 20–25 kPa) and low-normal (65–75 mmHg) vs. high-normal (80–100 mmHg) MAP [7, 8] during the first 36 h after ROSC in 123 comatose patients resuscitated from VF/VT OHCA. The investigators achieved clear separation in PaO_2, $PaCO_2$ and MAP between the groups but there was no difference in the values of neuron specific enolase (NSE), a biomarker of HIBI, at 48 h after ROSC. High-normal $PaCO_2$ and moderate hyperoxia increased regional cerebral oxygenation (rSO_2) but there were no differences between the groups in any of the secondary outcomes.

One of several reasons for the failure to replicate the findings of previous observational studies is the likely considerable heterogeneity in optimal targets among patients. Approximately a third of post-CA patients will lose cerebral autoregulation and are likely to require a higher MAP to preserve cerebral blood flow [9]. rSO_2 has been used to determine optimal MAP in post-CA patients but it is unknown how well rSO_2 correlates with cerebral perfusion pressure (CPP). Taccone and colleagues have used trans-cranial Doppler to assess middle cerebral artery mean flow velocities (MFVmca) in 30 post-CA patients to provide an estimate of CPP (eCPP) [10]. Lower eCPP values were found in non-survivors compared with survivors, while MFVmca, rSO_2 and MAP values were similar between groups. It is possible that strategies to optimize eCPP instead of MAP or rSO_2 may improve neurological outcome.

Prognostication

Prediction of neurological outcome in comatose resuscitated patients is challenging. Among indices for estimating severity of HIBI, NSE has several advantages: potential for blinded evaluation –

therefore avoiding a self-fulfilling prophecy bias – and no influence from sedation and TTM. However, in order to obtain a specificity close to 100% for prediction of poor outcome, very high levels are needed, and the consequent sensitivity is low. Moreover, NSE values are influenced by haemolysis [1].

In a substudy of the TTM trial, [11] a new biomarker - neurofilament light chain (NFL) – was assessed blindly for neuroprognostication after CA. At 24 h, a NFL value of 478 pg/mL predicted poor neurological outcome at 6 months with 69 [57-79]% sensitivity and 98 [96-100]% specificity. The area under the receiver operating characteristic curve was 0.94 (0.92−0.95), greater than that of any other predictor, including NSE, brain CT, somatosensory evoked potentials, EEG, and clinical examination. Unlike NSE, NFL blood values are not influenced by haemolysis.

Clinical examination is crucial for neuroprognostication and absence of standard pupillary light reflex (sPLR) at ≥ 72 h is recommended as a robust predictor of poor neurological outcome after CA [1]. However, sPLR is operator-dependent, qualitative and, since it cannot be concealed from the treating team, is prone to self-fulfilling prophecy bias. In a European 456-patient multicentre prognostication study [12] where the quantitative neurological pupil index (NPi) measured blindly using automated pupillometry was compared with sPLR, an NPi≤2 during the first 72h after ROSC had significantly higher specificity than an absent sPLR ($p < 0.001$). NPi predicted unfavourable outcome with 0% FPR as early as 24 h after CA. Among patients whose sPLR was scored as absent, those with false positives had a significantly smaller pupil size than those who had a poor neurological outcome (1.9±0.22 vs. 2.8±1.05 mm; $p=0.009$), suggesting that miosis may have prevented clinicians from detecting sPLR.

Neuroprognostication guidelines focus on the early post-resuscitation phase (72-96 h), while little is known about late predictors. In a multicentre prognostication study[13] fractional anisotropy (WWM-FA) measured on magnetic resonance imaging (MRI) was evaluated as a predictor of poor neurological outcome at 6 months in post-ROSC patients who had been unconscious for at least 7 days. A WWM-FA threshold of 0.91 was identified in a 150-patient derivation cohort as a prediction

and subsequently tested in a 50-patient validation cohort, where it showed 89.7 (75.8–97.1)% sensitivity and 100 (69.1–100)% specificity for prediction of poor outcome. Despite its complex measurement, WWM-FA is a promising predictor in late awakeners after CA.

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